REMARKS

Entry of the foregoing and further and favorable consideration of the subject application are respectfully requested and earnestly solicited.

As correctly stated in the Official Action Summary, Claims 1-53 are pending in the present application. Claims 1-53 stand rejected.

By entry of this amendment, original patent Claims 1-17 are still pending. Claims 18-53 are canceled, without prejudice to or disclaimer of the subject matter contained therein.

Original patent Claims 1 and 14 have been amended to correct antecedent basis issues pointed out by the Examiner. Accordingly, no prohibited new matter is believed to have been added.

Original patent Claim 16 has been amended to delete some members of the Markush group. These members have been introduced in new Claims 54-57. Accordingly, no prohibited new matter is believed to have been added.

Claim Objections

The Examiner objected to the amendments filed November 2, 2000, and August 27, 2001 as allegedly improper for failing to comply with 37 C.F.R. § 1.173. As previously added claims (*i.e.*, Claims 18-53) have been canceled, the objection is obviated. Accordingly, withdrawal of this objection is respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-53 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled for the treatment of adverse reactions caused by liposomes with an anti-inflammatory agent. The Examiner has argued that the presently claimed invention is not enabled, because Applicants have not set forth any rationale underlying the presently claimed invention and the specification contains only one working example using indomethacin.

Without conceding to the merits of this rejection and solely in an effort to expedite prosecution, Claims 18-53 have been canceled without prejudice or disclaimer by this amendment, thereby mooting this rejection as it applied to those claims. This rejection, as it applies to original patent Claims 1-17 and to new Claims 54-57, is respectfully traversed.

Applicants respectfully submit that a *prima facie* case of lack of enablement has not been adduced. The initial burden of setting forth a reasonable explanation as to why the scope of protection provided by any claim is not adequately enabled by the description of the invention provided in the specification is on the Office. *In re Wright*, 999 F.2d 1557, 1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). The standard for determining whether the enablement requirement has been met is whether the experimentation needed to practice the invention is undue or unreasonable. M.P.E.P. § 2164.01 referring to *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916). To object to a specification on the grounds that the disclosure is not enabling with respect to the scope of a claim sought to be patented, the examiner must provide evidence or technical reasoning substantiating those doubts. *Id.* and M.P.E.P. § 2164.04. Additionally, without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. *In re Wright*, 999 F.2d 1662, 27 U.S.P.Q.2d 1513; *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971). Such rejections should be based on an analysis of the *Wands* factors. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) and M.P.E.P. § 2164.01(a). However, it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the [*Wands*] factors, while ignoring one or more of the others. The examiner's analysis ***must consider all the evidence related to each of these factors***, and any conclusion of non-enablement must be ***based on the evidence as a whole***. *In re Wands*, 858 F.2d at 737 and 740, 8 U.S.P.Q.2d at 1404 and 1407.

An analysis of all of the *Wands* factors as they pertain to the claimed invention has not been performed. Additionally, the limited analysis performed did not view the ***evidence as a whole***. At best, the Examiner has merely addressed the breadth of the claims, which is merely a possible starting point for an enablement inquiry.

The Office Action further set forth that enablement was lacking, because only the working example of indomethacin was provided. First, Applicants point out that **compliance with the enablement requirement does not turn on whether an example is disclosed at all**. M.P.E.P. § 2164.02. An example may be "working" or "prophetic." *Id.* As is well understood, an applicant need not have actually reduced the invention to practice prior to filing the application. *Gould v. Quigg*, 822 F.2d 1074, 1078 and M.P.E.P. § 2164.02. Hence, the concept of a specification being a constructive reduction to practice. The complete lack of a working example is a factor only to be considered in a case involving unpredictable and undeveloped art. M.P.E.P. § 2164.02. However, an applicant need not describe all actual embodiments. *Id.*

By the Examiner's admission that "liposomes are known in the art as drug delivery agents for the past 20 years", Applicants submit that the technology is construed as ***neither unpredictable or undeveloped***. (Office Action, Paper No. 19, page 3). Accordingly, this specification would not be required to have even one example when the art is as developed and predictable as admitted in the Office Action. M.P.E.P. § 2164.02. Nevertheless, Applicants provide a working example with indomethacin.

Applicants further note that with the working example of indomethacin, an *in vivo* test system for evaluating the efficacy of anti-inflammatory agent is provided in Example 4. There is nothing inherently complicated for one skilled in the art to repeat this procedure dosing animals with other anti-inflammatory agents. The procedure and testing of other drugs would be routine.

According to M.P.E.P. § 2164.04, an examiner should make specific findings of fact, supported by the evidence and then drawing conclusions based on the findings of fact. Here, the Examiner's reasoning is confined to the lack of a rationale for the invention and to analogies to the use of anti-inflammatory agents ***for other purposes unrelated*** to the present invention (*i.e.*, the Examiner states that some anti-inflammatories have certain effects and others do not). These statements are irrelevant. The Examiner has provided no concrete reason why other anti-inflammatory agents could not be used according to the

invention or screened using the assay provided. Moreover, no official notice regarding the other anti-inflammatory agents has been taken, so the knowledge is not of notorious character. M.P.E.P. § 2144.03. If the rejection is being based on facts within the personal knowledge of the Examiner, then Applicants respectfully request that the facts be supported either by references or if those are unavailable, by an affidavit by the Examiner. *Id.* The conclusion that enablement is lacking is purely speculation that other anti-inflammatory agents might not have the same effect. Applicants respectfully submit that the Examiner must provide a reason to doubt the objective truth of the statements contained in the specification. M.P.E.P. § 2164.04. If one skilled in the art could determine which embodiments would be operative or inoperative with expediture of no more effort than is normally required in the art, then the claim is considered enabled. *Atlas Powder Co. v. E.I.duPont Nemours & Co.*, 750 F.2d 1569, 1577, 224 U.S.P.Q. 409, 414 (Fed. Cir. 1984), *See also, In re Angstadt*, 537 F.2d 498, 502-03, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976) (undue experimentation not involved in determining operability v. inoperability). Applicants also submit that the Examiner has provided no evidence that any embodiment using an anti-inflammatory agent other than indomethacin is inoperable.

Applicants respectfully submit that if the Examiner believes there is missing information (*e.g.*, no examples other than indomethacin), then the Examiner (1) must set forth why the art is unpredictable and undeveloped, (2) must identify what information is missing, and (3) must state why one skilled in the art could not supply the information without undue experimentation, in view of the assay provided in the present application. M.P.E.P. § 2164.04. As noted above, Applicants submit that it would not be difficult for one skilled in the art to duplicate the working example with other anti-inflammatory agents besides indomethacin based on the disclosure and the level of skill in the art.

The Examiner argues that Applicants have not provided any rationale for the concept that anti-inflammatory agents may correct the drop in blood pressure caused by liposome administration. Applicants have found no legal support for the proposition that an applicant must provide a theory for how the claimed invention works. The test for

enablement is not a model of how the invention works, but rather whether the experimentation needed is undue or unreasonable. *In re Wright*, 999 F.2d 1557, 1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993).

Applicants also direct the Examiner's attention to U.S. Patent No. 5,874,422 to Krause *et al.* This patent provides further proof that other anti-inflammatory agents besides indomethacin are capable of reducing the blood pressure drop caused by liposome administration. The Krause patent contains a working example wherein aspirin is also able to counter the blood pressure drop caused by liposome administration. As the Examiner is likely aware, indomethacin and aspirin are structurally unrelated, however, they are able to accomplish the goal of the presently claimed invention. Accordingly, Applicants respectfully submit that the present invention cannot be limited to indomethacin. Applicants note that the Krause patent, which issued after the priority date of the present application, is not being used to support the state of the art, but merely to provide the Examiner with data showing another operative embodiment of the present invention. These data could have been generated using the same techniques described in Example 4 of the present application.

In light of the foregoing and in the absence of specific information of why other anti-inflammatory agents could not be used according to the presently claimed invention, Applicants respectfully submit that a *prima facie* case of non-enablement has not been established. Accordingly, withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-17 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner argues that the recitations of "bilayer" in Claim 1 and "functional group" in Claim 14 lack antecedent basis. The Examiner also argues that the Markush group in Claim 16 is improper, because it contains overlapping terms.

By the present amendment, Claims 1 and 14 have been amended to correct the lack of antecedent basis. Claim 16 has been amended to delete some terms of the Markush

group, some of which have been added in the new dependent claims. In the event that the rejection is deemed to still apply to the remaining terms in Claim 16, Applicants respectfully point out that M.P.E.P. § 2173.05(h) indicates that overlapping terms may be acceptable and contains several examples. The Examiner has not provided any evidence or reasoning explaining why the terms in Claim 16 would lead to confusion or indefiniteness. Applicants believe that Claim 16, as amended, complies with 35 U.S.C. § 112, second paragraph. However, Applicants respectfully request that the Examiner contact the undersigned should he have additional suggestions for amending Claim 16. Accordingly, withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 102

1. Rejection of Claims 25-27, 45, 47, 53 under 35 U.S.C. § 102(b) over JP 60152414 or JP 63264517.

Without conceding to the merits of this rejection and solely in an effort to expedite prosecution, by the present amendment, Claims 25-27, 45, 47, and 53 have been canceled, thereby mooting this rejection. Withdrawal of this rejection is respectfully requested.

2. Rejection of Claims 18, 25, 28, 45, and 53 under 35 U.S.C. § 102(b) or (e) over Meybeck (USPN 5,443,389).

Without conceding to the merits of this rejection and solely in an effort to expedite prosecution, Claims 18, 25, 28, 45, and 53 have been canceled, thereby mooting this rejection. Withdrawal of this rejection is respectfully requested.

3. Claims 18, 19, 21, 23-25, 27, 33-36, 43-45, and 53 under 35 U.S.C. § 102(b) over Young (USPN 5,023,087).

Without conceding to the merits of this rejection and solely in an effort to expedite prosecution, by the present amendment, Claims 18, 19, 21, 23-25, 27, 33-36, 43-45, and 53 have been canceled, thereby mooting this rejection. Withdrawal of this rejection is respectfully requested.

Claim Rejections Under 35 U.S.C. § 103

1. Claims 18-32, 34-35, 41-42, 45, 47, and 53 under 35 U.S.C. § 103(a) over Young in combination with the JP references or Meybeck.

Without conceding to the merits of this rejection and solely in an effort to expedite prosecution, by the present amendment, Claims 18-32, 34-35, 41-42, 45, 47, and 53 have been canceled, thereby mooting this rejection. Withdrawal of this rejection is respectfully requested.

2. Claims 33-44 and 48-52 under 35 U.S.C. § 103(a) over Young in view of Park (*Biochim. Biophys. Acta* 1108:257-260 (1992)) or vice versa.

Without conceding to the merits of this rejection and solely in an effort to expedite prosecution, Claims 33-44 and 48-52 have been canceled, thereby mooting this rejection. Withdrawal of this rejection is respectfully requested.

3. Claims 29-32 and 46 under 35 U.S.C. § 103(a) over JP 63264517 or Young in view of Park or Park in view of Young or JP and in further view of Cheng (*Invest. Radiol.* 22:47-55 (1987)).

Without conceding to the merits of this rejection and solely in an effort to expedite prosecution, by the present amendment, Claims 29-32 and 46 have been canceled, thereby mooting this rejection. Withdrawal of this rejection is respectfully requested.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

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Date: September 23, 2002

Attachment to REPLY & AMENDMENT dated September 23, 2002

Marked-up Claims 1, 14, and 16

1. (Amended) A method of reducing a blood pressure decrease associated with the administration of a liposome to an animal which comprises incorporating a surface agent-modifying lipid comprising a phosphatidylethanolamine conjugated to a dicarboxylic acid into a liposome such at the surface agent-modifying lipid comprises at least about 2 mole percent of the lipid component of [the liposome's bilayer] a bilayer of the liposome and then administering the liposome to the animal wherein an anti-inflammatory agent is administered to the animal prior to administration of the liposome composition and wherein the liposome has an average diameter of from at least about 200 nm to about 5000 nm.

14. (Amended) The method of Claim [12] 13, wherein the functional group is a hydroxyl, thiol epoxide or amine group.

16. (Amended) The method of [claim] Claim 15, wherein the bioactive agent is a contrast agent, antibacterial agent, antiviral agent, antifungal agent, anti-parasitic agent, tumoricidal agent, [antimetabolite,] carbohydrate, polypeptide, peptide, [protein,] toxin, enzyme, hormone, neurotransmitter, glycoprotein, lipoprotein, [immunoglobulin,] immunomodulator, vasodilator, dye, radiolabel, [radio-opaque compound,] fluorescent compound, receptor binding molecule, anti-inflammatory agent, mydriatic compound, local anesthetic, narcotic, vitamin, [nucleic acid,] polynucleotide, nucleoside, or nucleotide[, MRI, radio or a water soluble iodinated contrast agent].

original = polynucleotide